UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/693,794	10/23/2003	Jerome B. Zeldis	9516-076-999	2021

20583 7590 09/10/2007

JONES DAY
222 EAST 41ST ST
NEW YORK, NY 10017

EXAMINER	
OLSON, ERIC	
ART UNIT	PAPER NUMBER
1623	

MAIL DATE	DELIVERY MODE
09/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/693,794	ZELDIS ET AL.	
	Examiner	Art Unit	
	Eric S. Olson	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,9,23 and 27-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,9,23 and 27-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *August 20, 2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This office action is a response to applicant's communication submitted July 9, 2007 wherein new claims 35-37 are introduced. This application claims benefit of provisional application 60/421003, filed October 24, 2002.

Claims 1-5, 9, 23, and 27-37 are pending in this application.

Claims 1-5, 9, 23, and 27-37 as amended are examined on the merits herein.

Applicant's arguments, submitted July 9, 2007, with respect to the rejection of instant claims 1, 6, and 15 under the doctrine of obviousness-type double patenting for claiming an invention not patentably distinguishable from claims 1, 5, 9, 22, and 23 of 5955476, have been fully considered and found to be persuasive to remove the rejection as the genus claimed in claim 1 of '476 does not include the claimed compound. Therefore the rejection is withdrawn.

Applicant's amendment, submitted July 9, 2007, necessitates the following new ground of rejection:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 37 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant's amendment submitted January 8, 2007 with respect to the aforementioned claims has been fully considered and but is deemed to insert **new matter** into the claims since the specification as originally filed does not provide support for a dose of active agent that is specifically "about 5 mg per day." Although the specification discloses ranges encompassing this dosage, it does not describe this particular dose, or provide any reason to specifically practice a dose of about 5 mg per day. As the instant specification as filed contains no description of this dosage level the specification as originally filed does not provide support for the subject matter of instant claims. See *in re Smith*, 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972). Because Applicant's amendment necessitated this new ground of rejection, the rejection is made **FINAL**.

The following rejections of record in the previous office action are maintained:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 9, 27-30, and 33-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Omoigui (US patent publication 20040038874, reference of record in

previous office action) in view of Olmarker et al. (PCT international publication WO02080891, of record in previous office action) Omoigui discloses a method for the treatment of persistent pain by administering a drug that antagonizes one or more mediators of inflammation. (p. 1, paragraph 0004) Drugs useful in this manner include TNF-α blockers, (p. 2, paragraphs 0007 and 0011) including thalidomide and analogues as a specific embodiment. (p. 3, paragraph 0023) Reflex Sympathetic Dystrophy, otherwise known as chronic regional pain syndrome, is listed as a disease treatable by this method. (pp. 9-10, paragraphs 0078-0082) Omoigui does not disclose a method using the specific compounds of the claimed invention in the specific dosage amounts listed, in the dosage forms of instant claims 27-30 and 33-34.

Olmarker et al. discloses a method of treating low back pain due to leakage of the nucleus pulposus from a damaged intravertebral disk, comprising administering a TNF inhibitor. (pp. 4-6) Because the mechanism of this pain involves the irritation of an affected nerve, it is considered to be a form of neuropathic pain. Specific compounds useful in the method of Olmarker et al. include thalidomide derivatives, including the compound CDC-501, which according to its chemical abstracts registry entry, is identical to the immunomodulatory compound 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione used in the claimed method. (p. 7, lines 24-26, see also chemical abstracts registry number 191732-72-6) The compound can be administered orally as a pill, syrup, or lozenge, (p. 9, lines 11-12) in an oral dose of 10-300 mg. (p. 9, line 20) The compounds can be administered in combination with other active agents. (p. 12, lines 4-7)

It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the therapeutic method of Omoigui using the compound 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione in the specific dosage amounts listed, in the dosage forms of instant claims 27-30 and 33-34. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Olmarker et al. discloses that the claimed compound is a TNF-α inhibitor and a thalidomide analog, and thus useful in the method of Olmarker. One of ordinary skill in the art would have been motivated to administer the compound orally and in combination with other active agents because these limitations are taught by Olmarker for this compound. One of ordinary skill in the art would have been motivated to administer a dosage of 5-50 mg because this dosage range overlaps substantially with the dosage range of 10-300 mg taught by Olmarker et al. One of ordinary skill in the art would have been motivated to administer the compound as a tablet or capsule because these dosage forms are similar to the pill and lozenge oral dosage forms taught by Olmarker. One of ordinary skill in the art would have been motivated to administer the compounds as a pharmaceutically acceptable salt, solvate, or stereoisomer because these pharmaceutically acceptable dosage forms are routine and well known in the art for compounds to be administered as pharmaceuticals. One of ordinary skill in the art would have reasonably expected success in using this specific compound because Olmarker et al. already discloses that the compound can be used to treat other TNF-dependant pain syndromes such as lower back pain. One of ordinary skill in the art would have reasonably expected success in using the specific claimed dosage form and

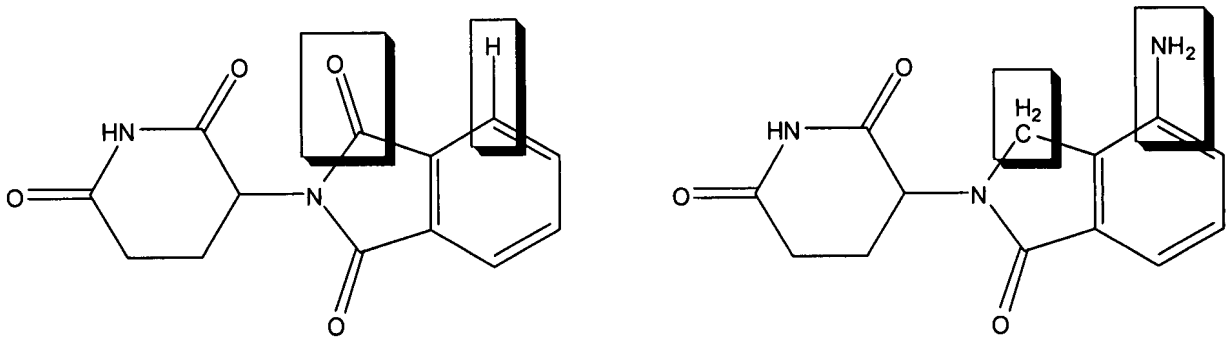
amounts because determining the exact details of the dosage form to be administered is well within the ordinary and routine level of skill in the art. With respect to the new dosage ranges of claims 33-35, one of ordinary skill in the art would have been motivated to test various dosages in order to optimize the therapeutic regiment for the particular disease being treated. (e.g. CRPS vs. low back pain) and the particular route of administration (e.g. oral vs. intravenous) This experimentation is merely routine and predictable.

Thus the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, submitted July 9, 2007, have been fully considered as they relate to the above ground of rejection, but are not persuasive to remove the rejection. Applicant argues that Omoigui does not disclose that thalidomide and its analogs can be used to treat complex regional pain syndrome but merely discloses that they inhibit TNF-alpha and other cytokines. However, this statement is in the context of a recitation of different classes of drugs that inhibit mediators of inflammation, and thus are useful for treating all sorts of pain, including complex regional pain syndrome. See in particular paragraphs 0004-0007 of Omogui and claims 1-3 of Omogui.

Applicant further argues that Omogui does not disclose what compounds are reasonably considered to be thalidomide analogs, and gives no guidance or working examples for determining these compounds or for selecting the specific claimed compound. However, the teaching of Olmarker that the claimed compound (referred to as CDC-501 by Olmarker) is a TNF-alpha inhibitor is sufficient to guide one skilled in the

art to realize that it can be used in the method of Olmarker. Given the close structural similarity between CDC-501 and thalidomide (see figure 1 below) one of ordinary skill in the art would immediately recognize that it is a thalidomide analog by any reasonable definition of the term "analog." This teaching that CDC-501 is a TNF-alpha inhibitor is sufficient to motivate one of ordinary skill in the art to substitute it for the generic "thalidomide analogs" of Omogui, especially since it is itself clearly a thalidomide analog.



Thalidomide CDC-501 Thalidomide Analog

Figure 1 - CDC-501 has the same carbon skeleton as thalidomide and only differs in the removal of one ketone and the adition of one amino group. It is reasonably considered to be a thalidomide analog.

Applicant further argues that Olmarker teaches away from the claimed dose ranges by providing preferred examples of a dosage range of 200-800 or 400-600 mg per day. However, as discussed above, one of ordinary skill in the art would have naturally experimented with different higher of lower dosage levels when treating a different disorder such as complex regional pain syndrome, in order to determine the optimal dosage level to use.

Finally, Applicant argues that no motivation has been provided for one of ordinary skill in the art to combine the prior art references. As discussed above, the motivation to combine the two references is that the compound CDC-501 is both a TNF-alpha inhibitor and a thalidomide analog, and thus a species of compound disclosed by Omogui to be useful for treating all types of pain, including complex regional pain syndrome. Seeing these teachings of the prior art, one of ordinary skill in the art would have recognized that the compound CDC-501 disclosed by Olmarker would produce a successful therapeutic effect in the method of Omogui.

Therefore the rejection is maintained and made **FINAL**.

Claims 2-5 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Omoigui (US patent publication 20040038874, reference of record in previous office action) in view of Olmarker et al. (PCT international publication WO02080891, of record in previous office action) in view of the Merck manual of diagnosis and therapy, seventeenth edition. (Herein referred to as Merck, of record in previous office action)

The disclosure of Omoigui in view of Olmarker et al. is discussed above. Omoigui in view of Olmarker et al. does not disclose a method further comprising administering the additional therapeutic agents of instant claims 2-5 or the therapies of instant claim 23.

Merck discloses that complex regional pain syndrome may be treated with several drugs including nifedipine, prednisone, opioid analgesics, tricyclic antidepressants, and anticonvulsants. (p. 1373, left column, second paragraph) It

should be noted that it is well known in the art that opioid analgesics include oxycodone, tricyclic antidepressants include amitryptyline, imipramine, and doxepin, and anticonvulsants include gabapentin. Merck also discloses that physical therapy is essential throughout therapy for complex regional pain syndrome (p. 1373, left column, last paragraph) and that pain relief that outlasts the administration of a sympathetic block but is still transitory suggests the need for surgery. (p. 1373, left column, second paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the method of Omoigui for the treatment of complex regional pain syndrome further comprising administering one or more of the pharmaceutical active agents described by Merck and still further administering physical therapy and/or surgery. One of ordinary skill in the art would have been motivated to combine these teachings because Omoigui and Merck both disclose their respective teaching as being useful for treating the same condition, namely complex regional pain syndrome. One of ordinary skill in the art would reasonably have expected success because combining two treatments known in the prior art to be effective for treating the same disorder by different methods is reasonably expected to produce at least additive effects.

Thus the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, submitted July 9, 2007, have been fully considered as they relate to the above ground of rejection, but are not persuasive to remove the rejection. Applicant's arguments with respect to this rejection are the same as those made with respect to the above rejection over Omogui in view of

Olmarker, and are not found persuasive for the same reasons. Therefore the rejection is deemed proper and made **FINAL**.

Claims 31 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Omoigui (US patent publication 20040038874, reference of record in previous office action) in view of Olmarker et al. (PCT international publication WO02080891, of record in previous office action) in view of Remington. (of record in previous office action)

The disclosure of Omoigui in view of Olmarker et al. is discussed above. Olmarker et al. does not disclose a method comprising administering the therapeutic compound in an enantiomerically pure form.

Remington discloses that different enantiomers of the same compound may possess different biological and pharmacological activities. (pp. 462-463)

It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the invention of Omoigui in view of Olmarker using enantiomerically pure 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione. One of ordinary skill in the art would have been motivated to practice the invention in this manner because, as Remington discloses that the two enantiomers of a chiral compound possess different activities *in vivo*, it stands to reason that one of the two enantiomers of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione possesses better activity and/or reduced side effects compared to the other enantiomer, and is thus a better drug in its enantiomerically pure form. One of ordinary skill in the art would

reasonably have expected success because testing two enantiomers for a known activity to determine which is the best drug candidate is a small and routine experimental burden well within the ordinary level of skill in the art.

Thus the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, submitted July 9, 2007, have been fully considered as they relate to the above ground of rejection, but are not persuasive to remove the rejection. Applicant's arguments with respect to this rejection are the same as those made with respect to the above rejection over Omogui in view of Olmarker, and are not found persuasive for the same reasons. Therefore the rejection is deemed proper and made **FINAL**.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 6, and 15 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over either claims 1, 4, and 8 of U.S. Patent No. 5635517 (Reference of record in previous action, herein referred to as '517) in view of Omoigui (US patent publication 20040038874, of record in previous office action) Claims 1 and 4 of '517 are drawn to methods of reducing undesirable levels of TNF-α in a mammal by administering the same compound recited in the instant claims. Said claims do not disclose a method of treating complex regional pain syndrome in this manner.

Omoigui discloses a method for the treatment of persistent pain by administering a drug that antagonizes one or more mediators of inflammation. (p. 1, paragraph 0004) Drugs useful in this manner include TNF-α blockers, (p. 2, paragraphs 0007 and 0011) including thalidomide and analogues as a specific embodiment. (p. 3, paragraph 0023) Reflex Sympathetic Dystrophy, otherwise known as chronic regional pain syndrome, is listed as a disease treatable by this method. (pp. 9-10, paragraphs 0078-0082)

It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the methods of claims 1 and 4 of '517 on a mammal suffering from complex regional pain syndrome. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Omogui discloses that blocking the action of TNF-α is an effective strategy for treating complex regional pain

syndrome. One of ordinary skill in the art would have reasonably expected success because Omogui et al. already demonstrates the utility of this method.

Response to Argument: Applicant's arguments, submitted July 9, 2007, have been fully considered as they relate to the above ground of rejection, but are not persuasive to remove the rejection. Applicant argues that the claims of '517 do not recite the specific disease Complex Regional Pain Syndrome or the specific compound recited in the instant claims, the claimed invention is patentably distinct from that of '517. However, as regards the specific compound of the instant claims, the species recited in claim 1 of '517 is very specific, having only eight possible embodiments. According to MPEP 2131.02, "When the compound is not specifically named, but instead it is necessary to select portions of teachings within a reference and combine them, e.g., select various substituents from a list of alternatives given for placement at specific sites on a generic chemical formula to arrive at a specific composition, anticipation can only be found if the classes of substituents are sufficiently limited or well delineated. Ex parte A, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990). If one of ordinary skill in the art is able to "at once envisage" the specific compound within the generic chemical formula, the compound is anticipated. One of ordinary skill in the art must be able to draw the structural formula or write the name of each of the compounds included in the generic formula before any of the compounds can be "at once envisaged." One may look to the preferred embodiments to determine which compounds can be anticipated. In re Petering, 301 F.2d 676, 133 USPQ 275 (CCPA 1962)." In the instant case, one of ordinary skill in the art would have clearly envisaged

all eight species included within the genus of claim 1 of '517. Furthermore, the species of the instant claims is in fact recited in claim 8 of '517, providing further anticipation of the specific species of claim 1.

As regards the specific disease species complex regional pain syndrome, Omogui discloses more than a general teaching that TNF-alpha inhibitors are useful for treating pain. As discussed above, Omogui discloses that complex regional pain syndrome/reflex sympathetic dystrophy is a specific pain disorder that can be treated by the disclosed method. Therefore, the claimed species are in fact taught by the applied references.

For these reasons the rejection is deemed proper and made **FINAL**.

Summary

No claims are allowed in this application. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Eric Olson
Patent Examiner
AU 1623
9/4/07

Anna Jiang
Supervisory Patent Examiner
AU 1623